Severe ulcerative colitis: predictors of response and algorithm proposal for rescue therapy

Introduction

Ulcerative colitis (UC) is characterized by chronic inflammation of the intestinal mucosa [1] and variable course [2]. While the aetiology of UC remains unclear, the hypothesis of a multifactorial genesis supposes that an antigenic stimulus may act as a "trigger" for an abnormal activation of the immune reaction towards colorectal mucosa [3, 4]. The intraluminal antigenic stimulation would facilitate the loss of the immunotolerance towards indigenous bacterial flora and consequently activates the gut-associated immune system [5].

Different courses characterize UC. In the more severe type, as a consequence of the impossibility to obtain the remission pharmacologically, about 30% of patients must undergo colectomy within three years from the onset of the illness [1, 6]. In this context, the first-line therapy is based on high dose intravenous steroids (the so-called Oxford Protocol) for 5-7 days that permit to obtain a 70% response rate [7]. The failure of this approach, defined as “steroid resistance”, has been considered for years as an absolute indication to colectomy [8]. In the last 20 years, a new rescue medical treatment has been included in this context aiming to reducing the need for surgery [9]. This rescue therapy provides a choice between cyclosporine A (CsA) and infliximab (IFX). The former administered intravenously, at a dose of 2-5 mg/kg/die, was the first rescue therapy being used [10], albeit in the last years several biologic drugs have become a powerful option in this setting [11]. The choice between these two options is arbitrary and depends on the physician’s experience. In literature, the only indication reported concerns the use of IFX in patients who have been previously treated for long time with azathioprine or whit hypomagnesemia, hypocholesterolemia and steroid-dependence [12].

While some reports suggested that rescue therapy can avoid short-term colectomy in patients treated for severe steroid-refractory UC [13], other studies did not confirm these data [14]. As a consequence, in the last decades, the colectomy rate for severe steroid-resistant UC has been barely constant, despite pharmacological advances [14]. In previous reports of our centre [15, 16] 60% of a cohort of patients with steroid-refractory colitis responded to CsA and 60% of these responders retained the colon after 1 year; these figures fell to 35% at 7 years but improved to 60% on AZA. The overall need for colectomy remains high in these patients and toxicity must be monitored.

The aim of our study was to identify predictors of response to IFX or CsA in patients with severe steroid refractory UC.

Material And Methods

Recruitment of participants

In a cross-sectional, retrospective study, we included 61 consecutive adult patients selected from the database of the inflammatory bowel diseases (IBD) Unit of the San Giovanni Antica Sede-Molinette Hospital, Turin, Italy, affected, from 2002 to 2013, by an acute attack of severe UC according to the Truelove and Witts index [17] (bloody stools per day >= 6 and temperature > 37.8 °C or heart rate > 90 or haemoglobin [Hb] < 10.5 g/dL or C-reactive protein [CRP] > 30 mg/L or erythrocyte sedimentation rate [ESR] > 30 mm/h). At baseline, the full Mayo score [18] was also calculated.

All included patients were affected by left sided or extensive UC. Those affected by UC limited to the rectum were excluded.

All patients underwent to, at least, a rectosigmoidoscopy at the time of the hospital admission and concomitant biopsy specimens to look for cytomegalovirus (CMV) and histological signs of Clostridium difficile (C. difficile). The patients that were still treated with medical therapy 6 months from severe UC onset underwent full colonoscopy.

We defined response to rescue therapy, based on IFX or CsA, a three or more points reduction in Mayo score after six months of therapy and the avoidance of colectomy 1 year after [19].

The population features extrapolated included: gender, age, time from UC diagnosis, months of steroid or/and azathioprine therapy before onset of the severe phase, smoking habits, extension of the disease, laboratory analyses in the acute phase (white blood cells [WBC], CRP, ESR, Hb), Mayo score and timing of surgery, in patients who needed colectomy.

Patients who underwent surgery for dysplasia, neoplasia, toxic megacolon and perforation were excluded from the study.

The study was conducted in accordance with ICHGood Clinical Practice guidelines, the Declaration of Helsinki, and local laws and regulations.

Statistical analysis

Arithmetic mean was calculated for variables with normal distribution (Gaussian distribution). For variables with a non-normal distribution geometric mean, obtained by the logarithmic transformation was reported. When the logarithmic transformation was not possible, due to the presence of 0 values, the median was calculated. For all data, the respective confidence interval (CI) and their range of values were reported; the CI was calculated at 95%. We considered data with $P < 0.05$ as statistically significant.

For parametric variables, the Independent sample t-test was used; for dichotomous variables in two independent samples, the Fisher exact test was used, and for dichotomous variables with more than two independent samples, the chi-square test was used.

When appropriate, the ability of a parameter to predict the response was evaluated using Receiver Operating Characteristic (ROC) curve analysis (Metz, 1978).

Multivariate logistic regression analysis has been used to identify predictors of response to therapy with IFX and CsA.

The intention to treat analysis was performed.

Data analysis was performed using MedCalc software (12.2.1.0 version).

Results

All 61 patients were admitted to the Hospital between 2002 and 2013.

At the admission, after diagnosis of severe UC at Truelove and Witts index and exclusion of precipitants conditions (C. difficile by stool analysis and CMV at sigmoidoscopy with biopsy), the patients were treated with systemic i.v. steroids (methylprednisolone 0.75–1 [mg/kg]); if inadequate clinical response at day 3-5 was obtained, IFX or CsA (rescue therapy) were administered, based on clinician preference. In patients who responded to rescue therapy, steroids were gradually tapered and administered orally until withdrawal in 2-3 months.

In 12 patients (19.7%), colectomy was performed in the first days of the admission due to impending toxic megacolon or impending intravascular disseminated coagulation (CID) and the rescue therapy were not administered.

Hence, the 49 patients (25 females) treated with rescue therapy were included in the study.

The mean age was 38 years (95% CI: 35.1 - 41.8), the range was 18 - 61.

All patients were navies to both IFX (or any other anti-Tumor necrosis factor agent) and CsA.

IFX was administered at the standard dose of 5 mg/kg given as an i.v. induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg i.v. every 8 weeks thereafter; CsA was administered at the 2 mg/kg/day i.v. for a week followed by oral administration at 4 mg/kg/day (dose adjustments were based on plasma levels, with a target concentration of 200-250 μg/mL).

Two patients treated with IFX and 1 treated with CsA suspended the therapy after the first administration because of an allergic reaction.

Regarding the treatment of patients who responded to rescue therapy, CsA was administered to 23 patients (10 females) and IFX to 15 patients (8 females).

In particular, 23 of 29 (79.3%) patients in the CsA group versus 15 of 20 (75%) patients in the IFX group avoided colectomy after 1 year (P = 0.87).

Eleven patients (6 receiving CsA and 5 IFX) did not respond to rescue therapy and underwent colectomy (Table 1).

Table 1

At the time of hospital admission, considering the 20 patients in which the rescue therapy was performed with IFX, 11 were previously treated with systemic steroids and 13 with azathioprine; between the 29 patients in which the rescue therapy was previously performed with CsA, 13 were treated with systemic steroids and 14 with azathioprine.

Predictors of response to therapy

Sex

There was no statistical difference between males and females in the response to either CsA ($P = 1$) or IFX therapy ($P = 0.3$) at the Fisher's exact test.

Mean age

Considering only patients treated with non-surgical approach, there was no difference in mean age comparing those treated with IFX (36 years; 95% CI: 29.4 - 42.4) versus those treated with CsA (40 years; 95% CI: 34.7 - 46.3) ($P = 0.8$).

Considering patients treated with IFX who responded to therapy, the mean age was 33 years (95% CI: 22.5 - 43.7) *versus* 38 years (95% CI: 27.8 - 47.7) of those who did not respond to therapy ($P = 0.5$).

The mean age of patients treated with CsA who responded to therapy was 39 years (95% CI: 31.5 - 46.4) *versus* 42 years (95% CI: 29.1 - 54.2) of those who did not respond ($P = 0.8$).

UC duration

The duration of the disease at the beginning of the acute phase did not show a normal distribution, and ranged from 0.1 to 38.8 years in the group treated with IFX and from 0.1 to 37 years in the group treated with CsA. Hence, the analysis was performed with logarithmic transformation. Patients treated with IFX tended to have a longer duration of disease than those treated with CsA (not statistically significant, $P = 0.1$).

In patients who received IFX, no significant difference was seen, in terms of duration of the disease, between those who responded to therapy and those who did not respond ($P = 0.6$). Similar results were observed in patients receiving CsA ($P = 0.5$).

Steroid therapy duration

Considering only patients treated with non-surgical approach, in those treated with IFX, the average duration of steroid therapy, before the onset of the acute phase, was 19 months (95% CI: 13.7 - 24.6; range 1 - 34), versus 15 months (95% CI: 9.6 - 19.5; range 0-36) in those treated with CsA ($P = 0.2$).

In patients who received IFX, no significant difference was seen ($P = 0.5$), in terms of average duration of steroid therapy, between those who responded to therapy (mean: 17.2 months; 95% CI: 6.0 – 28.3) and those who did not respond (mean: 20.4 months; 95% CI: 12.9–27.9). A similar result was observed in patients receiving CsA, with a mean of 12.5 months (95% CI: 6.4 - 18.7) in responders *versus* 12.8 months in non-responders (95% CI: 8.3 – 28.1) ($P = 0.3$).

Previous azathioprine therapy

On the basis of a previous or not treatment with azathioprine, there was no statistically significant difference between the group treated with IFX and that treated with CsA ($P = 0.14$). Moreover, in the IFX group, there was no significant difference in response ($P = 1$) between a previous treatment with azathioprine (8 non-responders and 5 responders) or not (1 non-responder and 1 responder) (**Fig1**).

Fig1

In the group treated with CsA, there was a trend towards a better response with respect to those with a previous treatment with azathioprine ($P = 0.08$) (**Fig2**).

Fig2

While in patients treated with IFX a previous therapy with azathioprine led to a reduction of 10% in the response, in those treated with CsA, the response to rescue therapy decreased by about 40%. ($P = 0.14$).

The duration of azathioprine therapy was significantly longer in patients treated with IFX than in those treated with CsA ($P = 0.03$). However, there was no statistical difference between responders and non-responders either in the group treated with IFX ($P = 0.8$) or in the group treated with CsA ($P = 0.2$).

Smoke

The distribution of non-smokers, ex-smokers (i.e. a person who claims to have smoked at least 100 cigarettes in his life, not to be smoking at the time of the interview and who had stopped smoking for more than six months – according to WHO) and active smokers, was not different (Chi-square test, $P = 0.6$).

There was no difference in response in the group treated with IFX (Chi-square test for trend, $P = 0.3$) or in the group treated with CsA (Chi-square test for trend, $P = 0.3$ for both), but grouping the patients in 2 groups, one of ex-smokers and the other one of active smokers or non-smokers, resulted that the ex-smokers group did not respond to IFX (6 non-responders *versus* 0 responders, statistically significant, $P = 0.03$). Instead, non-smokers or active smokers significantly responded to INF, with 6 responders and 3 non-responders ($P = 0.03$).

Regarding CsA, even after grouping, no statistically significant differences were observed.

UC extension

In the cohort treated with IFX there was no significant difference in terms of response to rescue therapy ($P = 1$) among patients with disease limited to the left colon (3 negative and 2 positive) *versus* those with a subtotal/total disease (6 negative and 4 positive). Also in the group treated with CsA, the difference was not statistically different ($P = 0.4$) between those with subtotal/total disease (11 positive and 4 negative responses) *versus* patients with disease localization restricted to the left colon.

WBC

WBC values in the acute phase had a mean of 10256 10^9/L (95% CI: 9271.9 - 11239.5), with a range between 5610 10^9/L and 18700 10^9/L (NV = 4000 - 10000 10^9/L). In IFX group, the distribution of WBC values was normal only after logarithmic transformation and ranged from 7000 to 16990 10^9/L. Also in CsA group, the distribution of WBC values was normal only after logarithmic transformation and ranged from 5610 to 18700 10^9/L. No statistically significant difference was observed ($P = 0.8$) when the two groups were compared. Even though there was no statistically significant difference (independent samples T-test with logarithmic transformation, $P = 0.4$), among patients with higher WBC count (geometric mean of patients who responded to rescue therapy was 10249 10^9/L, 95% CI: 7782 - 13497 10^9/L *versus* 8875 10^9/L, 95% CI: 6872 – 11460 10^9/in those who did not respond L), IFX therapy seemed to be more successful in the group with WBC > 10000 10^9/L; in this case, 4 out of 6 patients responded to therapy versus 1 out of 7 in the group with WBC < 10000 10^9/L.

In patients treated with CsA, there was no significant difference ($P = 0.9$) between the two groups which showed a similar response.

CRP

The CRP values in the acute phase had a normal distribution after logarithmic transformation and a range between 0.1 mg/L and 174 mg/L (NV < 5 mg/L). Both in IFX group and in CsA group, the value of CRP had a normal distribution after logarithmic transformation and a range of 0.1 - 166 mg/L and 0.1 - 174 mg/L,

respectively. Independent sample T-test with logarithmic transformation did not demonstrate a significant difference between the two groups ($P = 0.13$). In patients treated with IFX, there was no statistical difference of response (independent sample T-test with logarithmic transformation, $P = 0.4$). In the group treated with CsA, patients with higher CRP value showed a statistically significant response ($P = 0.02$). Studying the receiver operating characteristic (ROC) curve of CRP in function of the response, we established a cut-off of 3 mg/L. The sample treated with CsA showed a statistically significant difference in the response to therapy in relation to CRP value ($P = 0.03$). Furthermore, in group with CRP > 3 mg/L, the response to therapy was much higher (13 positive responses *versus* 2 negative ones) than in group with CRP < 3 mg/L (2 positive *versus* 4 negative) (**Fig3**).

Fig3

ESR and Hb

The distribution of the ESR in the acute phase was normal, the mean was 38.8 mm/h (95% CI: 30.4 - 47.2 mm/h), with a range between 1 and 108 mm/h (NV = 1 – 15 mm/h). The ESR had a mean value of 37.8 mm/h (95% CI: 22.3 - 53.4 mm/h) in patients treated with IFX and a mean value of 37.6 mm/h (95% CI: 17.7 - 57.5 mm/h) in patients treated with CsA. A normal distribution was observed in both cases. There was no significant difference in the distribution of the ESR in the two groups (Independent sample t-test, $P = 1$). In patients treated with IFX, there was no significant difference in ESR in terms of response ($P = 0.9$). Also in patients treated with CsA, there was not a significant difference ($P = 0.9$).

The mean Hb in the acute phase was 11.1 g/dL (95% CI: 10.5 - 11.8), with a range between 7.1 and 14.8 g/dL and a normal distribution (NV = 12 - 18 g/dL). The mean Hb was 11.5 g/dL (95% CI: 10.1 - 12.9 g/dL) in the group treated with IFX and 11.5 g/dL (95% CI: 10.4 - 12.5 g/dL) in the group treated with CsA. The distribution was normal in both cases. There was no significant difference in Hb distribution between the two groups (independent sample T-test, $P = 0.9$). In the sample treated with IFX, the group with positive response had an Hb mean lower (Hb = 10.9 g/dL, 95% CI: 7.2 - 14.5 g/dL) than the group of non-responders (Hb = 11.9 g/dL, 95% CI: 10.3 - 13.6 g/dL), but the difference was not significant ($P = 0.4$). Also in the group treated with CsA no statistically significant difference ($P = 0.9$) was observed in Hb mean between the group with positive response

(Hb = 11.6 g/dL, 95% CI: 10.5 - 12.7 g/dL) versus that with negative response (Hb = 11.7 g/dL, 95% CI: 8.5 - 14.8 g/dL).

Mayo score

Considering the scores, the Mayo score of patients treated with IFX had a mean of 10.3 (95% CI: 9.7-10.8) and ranged from 8 to 12, and that of subjects treated with CsA was 10.2 (95% CI: 9.8-10.6) with a range of 8 - 12. There was no statistically significant difference (independent samples T-test, $P = 0.9$) between the two groups. Concerning patients treated with IFX, there was a statistically significant difference (independent sample T-test, $P = 0.04$) in Mayo score based on the response. Responders had a mean Mayo score of 9.7 (95% CI: 8.6 - 10.7), lower than that of non-responders whose Mayo score was on average 10.7 (95% CI: 10.1 - 11.2). On the other hand, in the group treated with CsA, there was no significant difference (independent sample T-test, $P = 0.1$) in Mayo score regarding the response to therapy. However, the group that had a better response to therapy had a higher Mayo score (10.5 with 95% CI: 10 - 10.9) than the one that did not respond to therapy (9.7 with 95% CI: 8.8 - 10.7). Setting 10 as Mayo score cut-off in the ROC curve as a function of the response, 5 patients treated with IFX and Mayo score ≤ 10 responded to therapy *versus* 4 ($P = 0.3$), while among those with Mayo score >10, only 1 responded to therapy *versus* 5 who did not ($P = 0.3$). In patients treated with CsA and Mayo score ≤ 10, 7 patients responded to therapy and 7 did not, while in patients with Mayo score > 10, 8 responded to therapy and 1 did not ($P = 0.08$).

Mayo score, of the entire cohort, at six month follow-up did not have a normal distribution which ranged from 0 to 11 and had a median of 6 (95% CI: 3.2 - 9). Mayo score after IFX therapy had a normal distribution with a mean of 7.8 (95% CI: 5.8 - 9.7) and ranged from 2 to 11. Applying the T-test for matched data, there was a significant reduction ($P = 0.01$) in Mayo score related to the response to therapy: pre-therapy mean of 10.1 (95% CI: 9.5 - 10.6) to 6 month after starting therapy mean of 7.8 (95% CI: 5.8 - 9.7).

Mayo score after therapy with CsA did not have a normal distribution, with a range of 0 to 11, and a median of 4 (95% CI: 2 - 9). At the T-test for matched data, there was a significant reduction ($P < 0.0001$) in Mayo score related to response to therapy that decreased from a mean of 10.1 (95% CI: 9.7 – 10.6) to a mean of 5.1 (95% CI: 3.4 -6.8).

Mayo score and CRP

According to the previously analyzed data, we looked for a correlation between the response and CRP < 3 mg/L with Mayo score ≤ 10 and CRP > 3 mg/L with Mayo score > 10.

In the first case, among patients treated with IFX and negative CRP / moderate Mayo score, 4 patients had a good response to the therapy and 3 did not. In the second case among patients with positive CRP / severe Mayo score, a favourable outcome was reported in 2 *versus* 5 patients ($P = 0.6$). Of the 4 patients treated with CsA, negative CRP / moderate Mayo score, no one responded to therapy; in the ones with positive CRP / severe Mayo score, 15 were responders and 4 non-responders ($P = 0.008$). In the second case in patients treated with IFX and positive CRP with a severe Mayo score, 1 responded to therapy *versus* 3 who did not, while in the ones with negative CRP and / or a moderate Mayo score, 5 patients responded *versus* 5 ($P = 0.6$); within the group of patients treated with CsA and positive CRP and severe Mayo score, 6 subjects had a favourable outcome and 1 did not, whereas in the ones with negative CRP and / or moderate Mayo score, a favourable response was obtained in 9 versus 7 ($P = 0.3$) (**Fig4** and **Fig5**).

Fig4

Fig5

Multivariate analysis

To minimize the bias resulted from the retrospective nature of the study, we performed a multivariate logistic regression analysis of the predictors that resulted significantly linked to the response to rescue therapy.

In the IFX group, ex-smokers status (P = 0.046) and a severe Mayo score (P = 0.048) were predictors of lower response also at the multivariate analysis.

In the CsA groups a CRP > 3 mg/L was a predictor of higher response (P = 0.039) also at the multivariate analysis.

Discussion

Our study shows that some feature influenced rescue therapy outcome in this cohort of patients with severe active UC.

Considering IFX treatment, the two main observations that emerged were that ex-smokers did not respond to therapy, in comparison with active smokers and never smokers, and that patients with a severe Mayo score had a significant lower response rate.

Previous therapy with azathioprine did not reduce the probability of response. Based on literature data, in this group of patients, the biological drugs are preferred because, after their stopping (not before one year), patients can continue immunosuppressive therapy with higher probability of maintaining remission[12].

Considering the CsA treatment, patients with CRP ≥ 3 mg/L had a significant probability of response. The previous use of azathioprine, the presence of extraintestinal manifestations and a Mayo score >10 did not significantly influence the response to treatment.

The long-term colectomy rate, based on literature data, for severe steroid-resistant UC is about 30% despite the introduction of rescue therapies [20]. Similarly, in our study the probability of undergoing colectomy was 24% without treatment, 33.3% after IFX and 26% after CsA. Thus, rescue therapy is not able to reduce the definitive need of colectomy, but have the role to procrastinate it, permitting an elective surgery, with lower risks than an emergency surgery. Furthermore, in our study, among patients treated with CsA, patients underwent colectomy within the first 2 years after medical treatment, while in patients treated with IFX, the distribution of events was more delayed in time.

Some critical issues should be considered. The sample size is not very large and the retrospective design of this study represents a limitation: a significant percentage of patients were in steroid or immunosuppressive therapy at the time of the hospital admission. On the other hand this study represents the real world experience and the influence of previous therapy has been studied.

Patients treated with IFX tended to have a longer duration of disease than those treated with CsA, but this difference was not statistically significant (P = 0.1) and if the longer duration of disease in patients treated with IFX could reduce its efficacy is controversial [21].

This study directly compares, in a homogeneous single centre cohort, the characteristics of patients with severely active UC looking at features that could lead to choosing therapy with IFX or CsA, now entrusted to a single

doctor choose. In addition, our results suggest a potential algorithm for the therapeutic choice in patients with steroid-resistant or steroid-dependent severe UC: because of the limited number of patients in each group and the retrospective nature of the study, the algorithm is more a proposal to be validated in prospective, with larger a sample size, clinical studies than a scheme of immediate clinical application (**Fig6**).

Fig6

In conclusion, in ex-smokers the use of CsA could be advisable. In patients who never smoked or in active smokers who have never been treated with azathioprine, CsA or IFX can be chosen. In patients who never smoked or active smokers that have been treated with azathioprine, IFX could be advisable if Mayo score is ≤ 10 and / or CRP is negative, while we suggest to use CsA if Mayo score is > 10 and CRP is positive. Larger and prospective studies have to confirm these promising results.

Compliance with ethical standards

This article does not contain any studies with human participants performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Dignass A, Eliakim R, Magro F et al. (2012) European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 1: Definitions and diagnosis. J Crohns Colitis 6:965–990.

2. Peyrin-Biroulet L**,** Panés J, Sandborn WJ et al. (2016) Defining Disease Severity in Inflammatory Bowel Diseases: Current and Future Directions. Clin Gastroenterol Hepatol 14:348-354.e17.

3. Danese S, Fiocchi C. (2011) Ulcerative colitis. N Engl J Med 365:1713-1725.

4. Actis GC, Pellicano R. (2016) The pathologic galaxy modulating the genotype and phenotype of inflammatory bowel disease: co-morbidity, contiguity, and genetic and epi-genetic factors. Minerva Med 107:401-412.

5. Etchevers MJ, Aceituno M, Garcia-Bosch O et al. (2009) Risk factors and characteristics of extent progression in ulcerative colitis. Inflammatory Bowel Disease 9:1320-1325.

6. Tremaine WJ, Sandborn WJ. (1999) Practice guidelines for inflammatory bowel disease: an instrument for assessment. Mayo Clin Proc 74:495-501.

7. Travis SP, Stange EF, Lémann M et al. (2008) European evidence-based Consensus on the management of ulcerative colitis: Current management. J Crohns Colitis 2:24-62.

8. Bennis M, Tiret E. (2012) Surgical management of ulcerative colitis. Langenbecks Arch Surg 397:11-17.

9. Koltun WA. (2009) Role of medical rescue therapy in the management of acute severe ulcerative colitis: the surgical perspective. Expert Rev Gastroenterol Hepatol 3:325-327.

10. Campbell S, Travis S, Jewell D. (2005) CyclosporineA use in acute ulcerative colitis: a long-term experience. Eur I Gastroenterol Hepatol 17:79-84.

11. Rutgeerts P, Sandborn WJ, Feagan BG et al. (2005) Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 353:2462-2476.

12. Van Assche G, Vermeire S, Rutgeerts P. (2011) Management of acute severe ulcerative colitis. Gut 60:130-133.

13. Lees CW, Heys D, Ho GT et al. (2007) A retrospective analysis of the efficacy and safety of Infliximab as rescue therapy in acute severe ulcerative colitis. Aliment Pharmacol Ther 26:411-419.

14 Mocciaro F, Renna S, Orlando A et al. (2012) CyclosporineA or Infliximab as rescue therapy in severe refractory ulcerative colitis: Early and long-term data from a retrospective observational study. J Crohns Colitis 6:681-686.

15. Actis GC, Fadda M, David E et al. (2007) Colectomy rate in steroid-refractory colitis initially responsive to cyclosporin: a long-term retrospective cohort study. BMC Gastroenterol 7:13.

16. Pinna-Pintor M, Arese P, Bona R et al. (2000) Severe steroid-unresponsive ulcerative colitis: outcomes of restorative proctocolectomy in patients undergoing cyclosporin treatment. Dis Colon Rectum 43:609-613.

17 Truelove Sc, Witts Lj. (1955) Cortisone in the treatment of ulcerative colitis. Final report of a therapeutic trial. Br Med J 2:1041–1048.

18. Schroeder KW, Tremaine WJ, Ilstrup DM. (1987) Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 317:1625-1629.

19. Subramaniam K, Richardson A, Dodd J et al. (2014) Early predictors of colectomy and long-term maintenance of remission in ulcerative colitis patients treated using anti-tumour necrosis factor therapy. Intern Med J 44:464-70.

20. Aratari A, Papi C, Clemente V et al. (2008) Colectomy rate in acute severe ulcerative colitis in the Infliximab era. Dig Liver Dis 40:821-826.

21. Nuij V, Fuhler GM, Edel AJ et al. (2015) Benefit of Earlier Anti-TNF Treatment on IBD Disease Complications? J Crohns Colitis. 9:997-1003.

Table 1. Patients' distribution.

61 PATIENTS IN TOTAL			
	RESCUE THERAPY (P = 0.87*)		NO RESCUE THERAPY
	INFLIXIMAB	CYCLOSPORINE A	
NO COLECTOMY	15 (75% of R.T.)	23 (79.3% of R.T.)	
COLECTOMY	5	6	12 (19.7% of total)

* not statistically significant; R.T. = Rescue Therapy

Fig1 Response to therapy with Infliximab according to the previous use or not of Azathioprine

Fig2 Response to therapy with Cyclosporine A according to the previous use or not of Azathioprine

Fig3 Response to therapy with Cyclosporine A based on the values of C - RP before therapy

Fig4 Predictors of response to Infliximab

Fig5 Predictors of response to Cyclosporine A

Fig6 Proposed treatment algorithm to be validated in larger, prospective studies